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Estimating Health Risk from Exposure to 1,4-Dioxane in Japan

Ryoji Makino*, Hajime Kawasaki, Atsuo Kishimoto,
Masashi Gamo and Junko Nakanishi

Research Center for Chemical Risk Management,
National Institute of Advanced Industrial Science and Technology
16-1 Onogawa, Tsukuba, Ibaraki 305-8569, Japan

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Exposure to 1,4-dioxane from the atmosphere around high-emission plants and from consumer products used in daily life that contain the substance may have adverse health effects; however, its emission into the atmosphere is not regulated. In this study, the health risk posed by 1,4-dioxane is assessed to investigate whether measures should be undertaken to reduce exposure to 1,4-dioxane. The notion of the margin of exposure (MOE), given by the ratio of no observed adverse effect level (NOAEL) to actual or projected exposure level, is used to assess risk. In exposure assessment, two types of exposure channel are considered: (a) the use of consumer products that contain 1,4-dioxane and (b) the inhalation of air around high-emission plants. To estimate exposure via channel (a), we measured the concentration of 1,4-dioxane in consumer products and estimated the interindividual variability of exposure by Monte Carlo simulation that reflects the measured data. To estimate exposure via channel (b), we employed a local-level atmospheric dispersion model to estimate the concentration of 1,4-dioxane immediately around high-emission plants. For hazard assessment, we derived the inhalatory and oral NOAELs for liver adenomas and carcinomas and the uncertainty factor. The results suggest that measures are not needed to reduce exposure to 1,4-dioxane from consumer products. As for inhalation exposure around high-emission plants, some residents may be exposed to health risks if certain conservative analytical conditions are assumed. Even in this case, we conclude that it is not necessary for Plant A to stop the use of 1,4-dioxane immediately and that medium- to long-term emission reduction measures should be sufficient.

*E-mail: ryoji-makino@aist.go.jp

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1. Introduction

1,4-dioxane is a synthetic organic compound that is widely used as an industrial solvent. The substance is regarded as a carcinogen in test animals, and is classified as Group B2 (probable human carcinogen) by the US Environmental Protection Agency and as Group 2B (possible human carcinogen) by the International Agency for Research on Cancer. The World Health Organization proposes that the concentration of 1,4-dioxane in drinking water should be 50 μg/L or below.(1) Both the Japanese government's quality standard for drinking water(2) and the guideline concentration for the water environment to be monitored(3) are 50 μg/L.

Meanwhile, a pollutant release and transfer register (PRTR) survey shows that the total annual emissions of 1,4-dioxane into the atmosphere are greater than those into the aquatic environment.(4) In 2001, the former were 160 tons, and the latter were 23 tons; in 2002, 184 tons and 64 tons; in 2003, 169 tons and 80 tons, respectively. Emissions from only two plants accounted for 70–90% of the total emissions to the atmosphere. They were pharmaceutical Plant A in Hikari, Yamaguchi Prefecture ("Plant A") and chemical Plant B in Daito, Shizuoka Prefecture ("Plant B"). The people who reside near these plants are likely to be exposed to high concentrations of 1,4-dioxane. However, the emission of this substance into the atmosphere is not regulated.

It is likely that we are continually exposed to 1,4-dioxane when using everyday consumer products such as shampoo and dishwashing liquids, which contain several kinds of surfactant. These surfactants contain 1,4-dioxane as a reaction by-product, although there are no data on the concentrations of 1,4-dioxane in consumer products except the data from a previous study.(5) The levels of 1,4-dioxane in consumer products are similarly not under official regulation.

The purpose of this study is to investigate whether 1,4-dioxane exposure-reduction measures should be undertaken in Japan. To do this, the health risk from exposure to 1,4-dioxane by the Japanese population was assessed using the notion of margin of exposure (MOE). MOE is calculated by dividing the no observed adverse effect level (NOAEL) by the actual or projected exposure level. When MOE is equal to or higher than the uncertainty factor, the risk of exposure to 1,4-dioxane is of minimal concern. If MOE is lower than the uncertainty factor, susceptible individuals may suffer from adverse health effects, therefore, risk reduction measures are needed.(6)

To calculate MOE, we estimated the exposure level to 1,4-dioxane and determined its NOAEL. To assess exposure, two kinds of exposure channels were considered. They were (a) the use of consumer products that contain surfactants and (b) the inhalation of air around high-emission plants. In (a), we measured the concentrations of 1,4-dioxane in consumer products that were sold in August 2003 (and are still sold at present) and estimated the interindividual variability of exposure by Monte Carlo simulation using the obtained concentrations. For (b), we used a local-level atmospheric dispersion model to estimate the concentrations of the substance in the vicinity of the plants. In the hazard assessment, we comprehensively reviewed the relevant literature and determined the endpoint and the NOAEL.

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In §2, we estimate the exposure to 1,4-dioxane. In §3, we describe the hazard assessment process, including the NOAELs. In §4, we calculate the MOE using the estimated exposure and the NOAELs to characterize the risk. §5 contains the discussion and conclusions.

2. Estimation of Exposure

2.1 *Exposure from use of consumer products*

As mentioned in the previous section, 1,4-dioxane is generated as a reaction by-product when manufacturing several kinds of surfactant. The two mechanisms for 1,4-dioxane generation are given below. 1,4-dioxane is generated by (i) cyclization reactions during the sulphonation step in alkyl ether sulphate (AES) manufacturing[7] and (ii) the polymerization of ethylene oxide under acidic conditions during the manufacture of, for example, alcohol ethoxylate (AE). However, the quantity of 1,4-dioxane generated by mechanism (ii) is expected to be small, because, in the most common manufacturing process of AE, ethylene oxide is polymerized by mixing it with an alkali catalyst.

We estimated the interindividual variability of 1,4-dioxane exposure from consumer products which contain surfactants such as AES and AE using a Monte Carlo simulation. The steps in the estimation were as follows. First, we measured the concentrations of 1,4-dioxane in various consumer products. Second, we constructed a simple model on the basis of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[8] to estimate exposure. The model contains several parameters, such as the concentration of 1,4-dioxane in a consumer product and the amount of the product used per application. Third, we assumed that each of the parameters had a probability distribution. Except for the concentration of 1,4-dioxane in a product, the population parameters such as mean and variance were obtained from previous studies (references are in Table 2). Fourth, the exposure to an individual was calculated by drawing random numbers from the assumed distributions and substituting them for the corresponding parameters. Finally, we iterated the previous step 10,000 times. The 4th and 5th steps were conducted using Crystal Ball® 2000 (Decisioneering, Inc.).

2.1.1 *Measurement of 1,4-dioxane concentrations in consumer products*

We bought consumer products at a drugstore in Tsukuba City in August 2003 and collected samples from these products. The samples were diluted with water and then injected into the purge-and-trap gas chromatography/mass spectrometry system. The apparatus was as follows: gas chromatography/mass spectrometry system: QP-5000 (Shimadzu Co.), purge and trap sampler: LSC-2000 (Tekmer), column: AQUATIC (I.D.0.25 mm × L.60 m × 1.0 μm, GL Sciences Inc.), absorbent trap: VOCARB3000 (Supelco, Inc.). The analysis was carried out by Shimadzu Techno-Research Inc. The measurement results are shown in Table 1.

1,4-Dioxane was detected in numerous AES-based products. The concentrations ranged from below the determination limit to 51 mg/L. All concentrations in AE-based products were below the determination limit. This does not necessarily mean that AE-based products do not contain any 1,4-dioxane. However, in view of the above measurement results and the way AE is produced, the quantity of 1,4-dioxane in AE is likely to be significantly smaller than that in AES.

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Table 1
Concentrations of 1,4-dioxane in various consumer products.

Product	Primary ingredient	Concentration[a] (mg/L)
Shampoo 1	AES[b]	41*
Shampoo 2	AES	9.5*
Shampoo 3	AES	5.5*
Shampoo 4	AES	9.1*
Shampoo 5	Lauramidopropylbetaine	n.d. (<10*)
Liquid soap 1	AES	n.d. (<5*)
Liquid soap 2	AES	n.d. (<5*)
Dishwashing liquid 1	AES	n.d. (<10)
Dishwashing liquid 2	AES	51
Dishwashing liquid 3	AE[c]	n.d. (<5*)
Dishwashing liquid 4	LAS[d], AE	n.d. (<10)
Laundry detergent 1	AE	n.d. (<10)
Laundry detergent 2	LAS, AE	n.d. (<5*)
Laundry detergent 3	Fatty acid salt, LAS, AE	n.d. (<5*)
Laundry detergent 4	AE	n.d. (<25)
Detergent for bath 1	AES	n.d. (<5)
Detergent for bath 2	AOS[e]	n.d. (<2.5)
Detergent for bath 3	SAS[f]	6.4
Detergent for car 1	Unknown	n.d. (<2.5)
Detergent for car 2	Anionic surfactant	38

[a] The unit of figures with "*" is mg/kg. "n.d." means not determined and figures in parentheses are determination limits; [b]Alkyl ether sulphate; [c]Alcohol ethoxylate; [d]Linear alkylbenzene sulphonate [e]Alpha-olefin sulphonate; [f]Secondary alkane sulfonate.

2.1.2 *Models and parameters*

Exposure from the use of shampoos and dishwashing liquids was estimated, because these products are frequently used and contact the skin directly. 1,4-Dioxane was assumed to enter the body through both inhalation and dermal absorption. The inhalation exposure from shampoo use, $E_{S,Inh}$, was estimated according to

$$E_{S,Inh}[\mu g/kg/day] = \frac{C_{B,air}[\mu g/m^3] \times I[m^3/h] \times T[h] \times N_S[/day]}{BW[kg]} \quad \text{(model 1)} \qquad (1)$$

$$C_{B,air}[\mu g/m^3] = \frac{W[kg] \times C_S[\mu g/kg] \times E[-]}{S[m^2] \times H[m]}, \qquad (2)$$

where $C_{B,air}$ is the concentration of 1,4-dioxane in the atmosphere in a bathroom, I is the inhalation rate, T is hours of shampoo use per application, N_S is the number of shampoo applications per day, BW is average human body weight, W is the volume of shampoo used per application, C_S is the concentration of 1,4-dioxane in shampoo, E is the evaporation rate of 1,4-dioxane from the shampoo, S is the floor area of the bathroom, and H is its ceiling

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Table 2
Assumptions on distribution of simulation parameters.

Parameter		[unit]	Distribution	Reference*
W	Volume of shampoo used per application	[kg]	Lognormal (GM = 0.0055, GSD = 1.6)	—
N	Number of shampoo applications per day	[/day]	Uniform (Minimum = 0.0, Maximum = 3.0)	—
C_S	Concentration of 1,4-dioxane in shampoo	[mg/kg]	Lognormal (GM = 8.8, GSD = 2.8)	—
F	Fraction of substance remaining on skin	[%]	Lognormal (GM = 3.0, GSD = 2.0)	(8)
A	Absorption rate from skin	[%]	Uniform (Minimum = 1.0, Maximum = 5.0)	(9)
BW	Average human body weight	[kg]	Lognormal (GM = 50, GSD = 1.35)	(10)
I	Inhalation rate	[m^3/h]	Uniform (Minimum = 0.50, Maximum = 1.5)	(8)
T	Hours of shampoo use per application	[h]	Uniform (Minimum = 1/60, Maximum = 15/60)	—
E	Evaporation rate of 1,4-dioxane from shampoo	[%]	Lognormal (GM = 10, GSD = 1.7)	(11)
S	Floor area of bathroom	[m^2]	Lognormal (GM = 3.03, GSD = 1.31)	(12)
H	Ceiling height of bathroom	[m]	2.5 (constant)	—

*"—" means that we were unable to acquire any information on the distribution of the corresponding parameter. We therefore assumed the distribution, the mean level, and the variation that were most likely to be appropriate. For (8)–(12), each study shows only a single value for the parameter. We therefore assumed the most likely and appropriate distribution and variation.

height. The assumptions on the distribution of each parameter are shown in Table 2.

The dermal exposure from shampoo use, $E_{S,Derm}$, was estimated according to

$$E_{S,Derm}[\mu g/kg/day] = \frac{W[kg] \times N_S[/day] \times C_S[\mu g/kg] \times F[-] \times A[-]}{BW[kg]}, \text{ (model 2)} \quad (3)$$

where F is the fraction of the substance remaining on the skin, and A is the absorption rate from the skin. The assumptions on the distribution of each parameter are shown in Table 2.

The geometric mean (GM) and geometric standard deviation (GSD) of the concentration of 1,4-dioxane in shampoos are acquired from the actual measurements, where the concentrations shown as "n.d." in Table 1 are replaced by half of the determination limit.

The inhalation and dermal exposures from the use of dishwashing liquid were also estimated using model 1 and 2 in which the words "shampoo" and "bathroom" were replaced by "dishwashing liquid" and "kitchen," respectively. As for the distribution of parameters, only the "number of applications per day" was changed. It was assumed that the parameter had a uniform distribution with a minimum of 0 and a maximum of 5. A histogram of the estimated exposure is illustrated in Fig. 1, and the key statistics are shown in Table 3.

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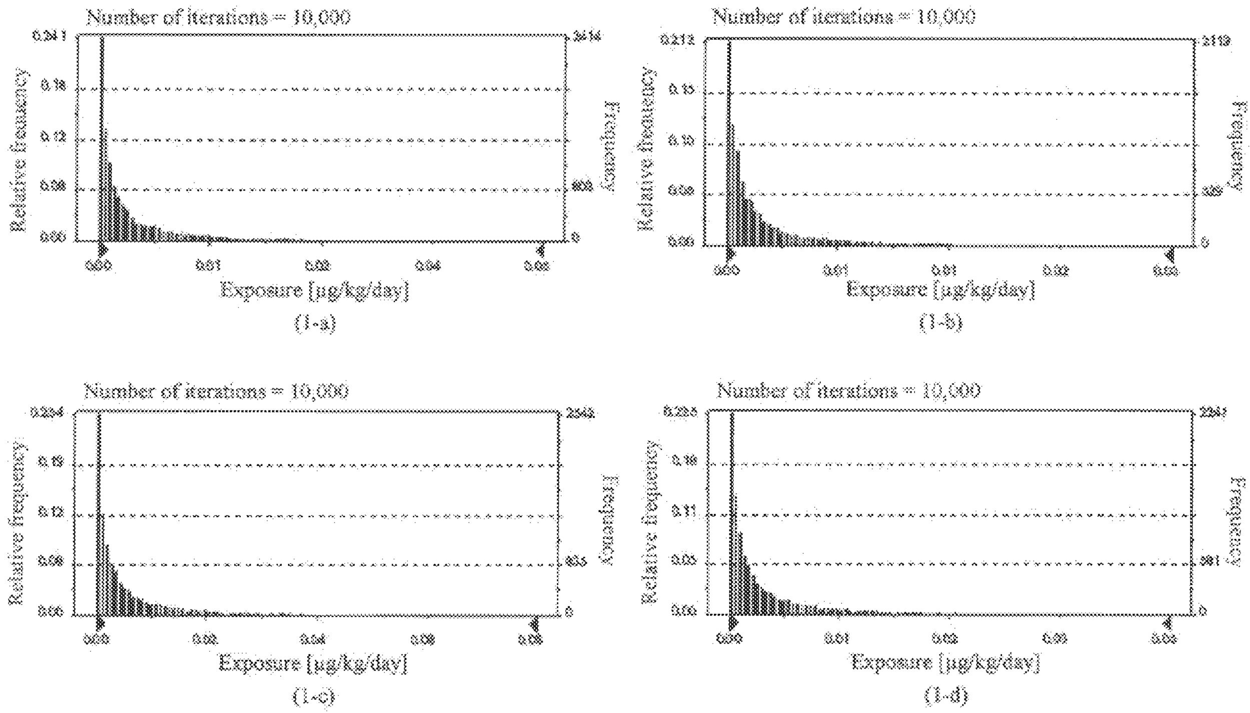

Fig. 1. Interindividual variation in exposure to 1,4-dioxane from use of shampoos and dishwashing liquids; (1-a): inhalation exposure from shampoo; (1-b): dermal exposure from shampoo; (1-c): inhalation exposure from dishwashing liquid; (1-d): dermal exposure from dishwashing liquid.

Table 3
Summary of simulation results of exposure from use of consumer products.

		Exposure (μg/kg/day)				
		Average	Median	Standard deviation	5th percentile	95th percentile
Shampoo	Inhalation	5.7×10^{-3}	1.6×10^{-3}	1.5×10^{-2}	7.2×10^{-5}	2.3×10^{-2}
	Dermal	3.4×10^{-3}	1.0×10^{-3}	8.6×10^{-3}	4.9×10^{-5}	1.4×10^{-2}
Dishwashing liquid	Inhalation	1.0×10^{-2}	2.8×10^{-3}	2.8×10^{-2}	1.1×10^{-4}	4.0×10^{-2}
	Dermal	5.8×10^{-3}	1.7×10^{-3}	1.5×10^{-2}	7.8×10^{-5}	2.4×10^{-2}

2.2 *Exposure from atmosphere around high-emission plants*

The PRTR survey in 2001 showed that the total emissions of 1,4-dioxane into the atmosphere were about 160 tons. The two highest-emission plants, A and B, annually emitted 79 tons and 27 tons of 1,4-dioxane into the atmosphere, respectively. It is likely that the residents around these plants absorb more 1,4-dioxane (therefore, are at higher risk) than residents in other areas. Hence, to quantify the exposure and assess their risk, the concentrations of the substance in the atmosphere around those plants were estimated in detail using the Ministry of Economy, Trade and Industry Low-rise Industrial Source

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dispersion model (METI-LIS) (Ver. 2.00).

METI-LIS is a local atmospheric dispersion model designed to investigate the effects of relatively low stacks, nearby buildings and other ground-level objects. It can be used to obtain short-term concentrations under fixed meteorological conditions or long-term concentrations as an annual average, based on the data from an automated meteorological data acquisition system (AMeDAS).

In this study, the AMeDAS data for 2001 were applied as meteorological conditions for estimating the annual average concentrations of 1,4-dioxane in the atmosphere around the plants. Although we did not know the precise conditions around the plants, we could acquire the data at the two meteorological observatories nearest to each plant as an approximation. These were the Kudamatsu and Yanai observatories for Plant A and the Fukuda and Omaezaki observatories for Plant B. The meteorological conditions around Plant A were estimated to be more comparable to those at the Kudamatsu observatory than those at the Yanai observatory because the directions of the sea and mountains as seen from the Kudamatsu observatory (the Yanai observatory) are the same as (almost opposite to) those from Plant A. For Plant B, the meteorological conditions around the plant were estimated to be more comparable to those at the Fukuda observatory on the basis of the similarity of the geographical conditions. Although the meteorological data from the Kudamatsu observatory and the Fukuda observatory are expected to be better in estimating the concentrations of 1,4-dioxane around each plant, we used the data from the Yanai observatory and the Omaezaki observatory, also, as a precautionary measure. The concentrations around Plant A from the Kudamatsu observatory data and from the Yanai observatory data were estimated separately. The concentrations around Plant B were estimated similarly.

The estimation was conducted on the basis of the following assumptions. (1) According to the PRTR survey results in 2001, the annual emissions of Plant A were 79 tons and those of Plant B were 27 tons. There were no emission sources other than these plants. (2) The emissions per hour were constant throughout the year. Hence, the emission rate was 9 kg/h for Plant A and 3 kg/h for Plant B. (3) The height of the stack was 5 or 10 m (estimates were made for both cases).

The concentrations in the atmosphere were estimated at 50-meter intervals along horizontal (east-west) and vertical (north-south) lines, and 1.5 meters above the ground. As shown in Fig. 2, we refer to each intersection of the horizontal and vertical lines, where concentration was estimated, as a "calculation point."

2.2.1 *Plant A*

Figure 3 shows the wind roses for the Kudamatsu and Yanai observatories. A wind rose is a diagram designed to show the distribution of wind direction experienced at a given location over an extended period. It is constructed on the basis of data for wind direction and velocity observed every hour. The solid line in the diagram indicates the distribution of the wind direction [%], and the dashed line indicates the annual average wind velocity [m/sec]. For example, at the Kudamatsu observatory, 20% of the wind observed in 2001 was easterly, with an average velocity of about 3 m/sec.

The estimated concentration maps are shown in Fig. 4, and the estimation results are summarized in Table 4. The "unconditional maximum concentration" in Table 4 means the highest concentration among the estimated annual average concentrations at all calculation

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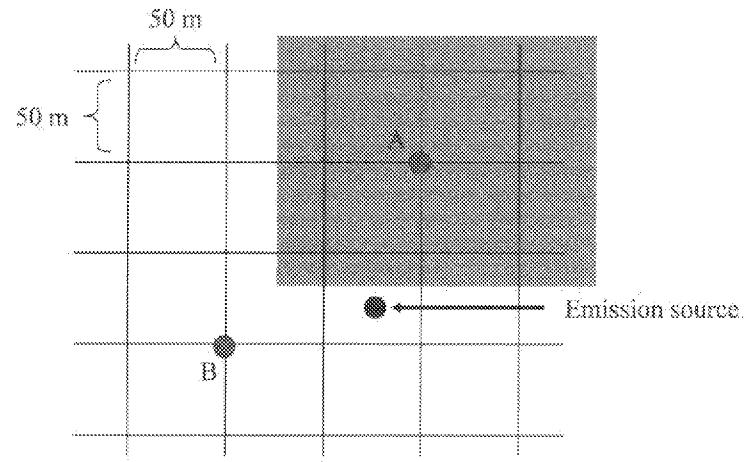

Fig. 2. Calculation points and residential zone. The concentrations are estimated at each intersection, such as points A and B. The shaded area represents a residential zone. If the estimated concentration at point A is higher than the concentraions at other intersections included in the residential zone, "the maximum concentration in the residential zone" is the concentration at point A.

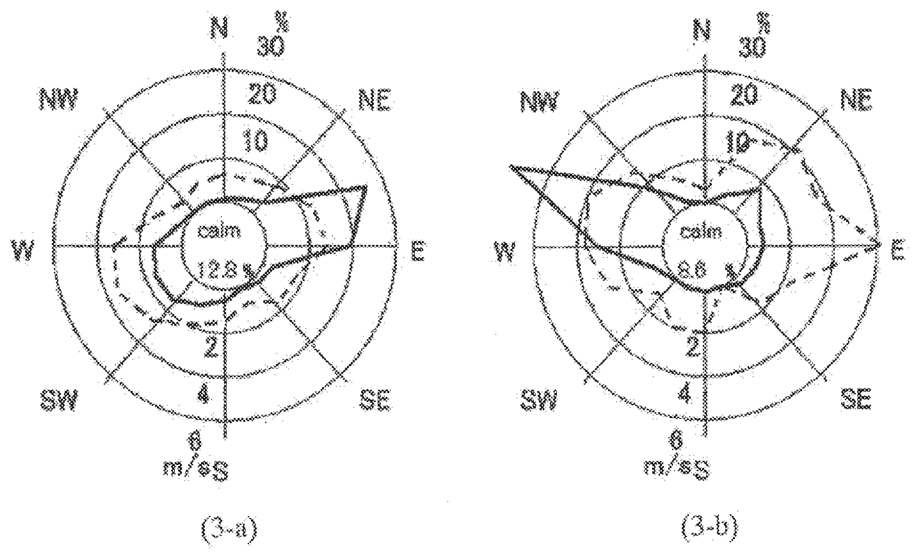

Fig. 3. Wind roses for (3-a) Kudamatsu and (3-b) Yanai in 2001. The solid line indicates the wind direction [%]. The dashed line indicates the annual average wind velocity [m/sec].

points. To estimate the exposure to 1,4-dioxane, it is necessary to obtain the concentrations at locations where people reside. They are expressed as the "maximum concentration in the residential zone" in Table 4. This means the highest concentration among the estimated concentrations for calculation points that are included in locations where people reside (Fig. 2).

In the case of a 10-meter (5-meter) stack, the maximum concentration in the residential zone using the data from the Yanai observatory was 22-fold (32-fold) higher than that for the data at the Kudamatsu observatory. This difference in estimated concentrations in

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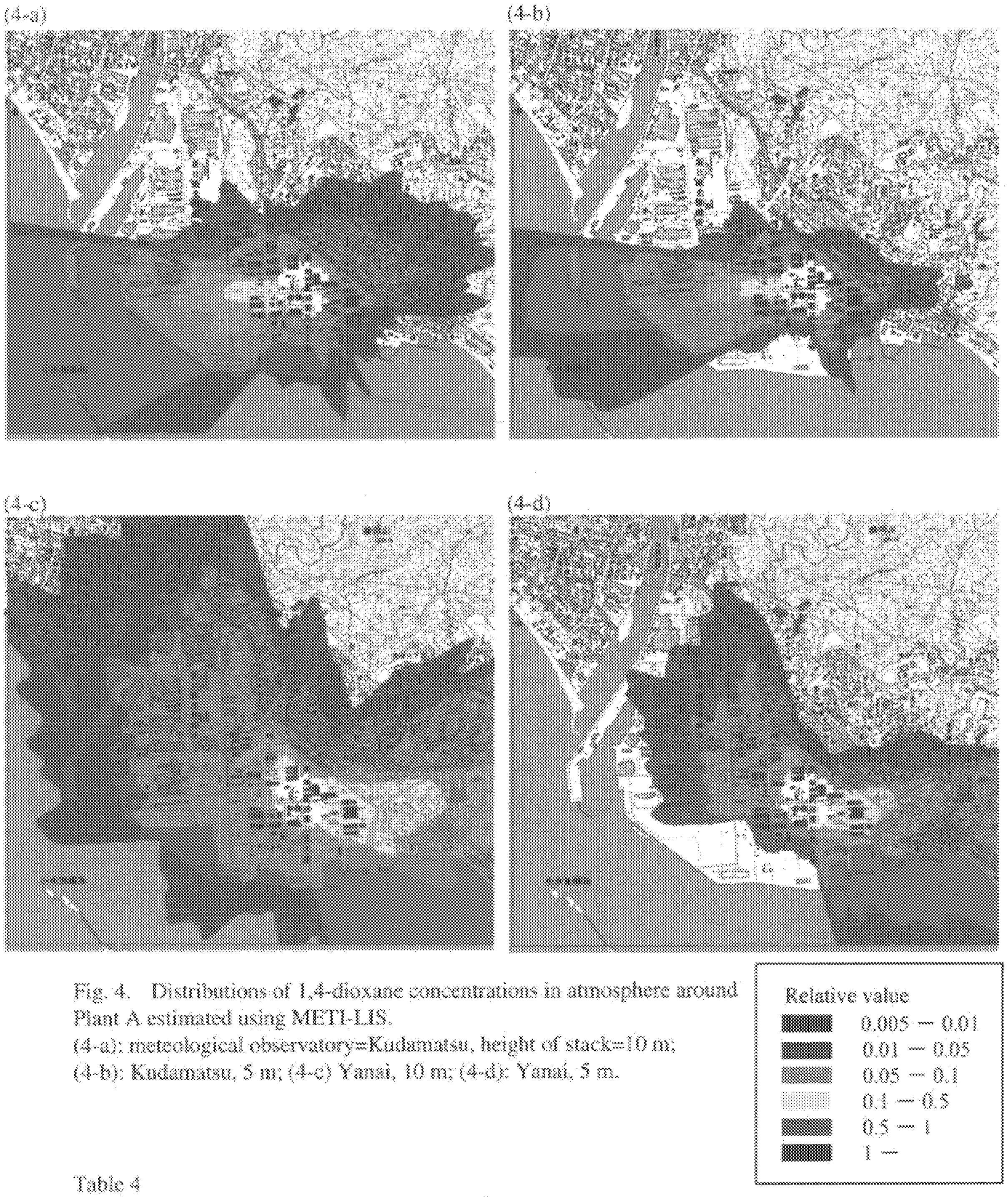

Fig. 4. Distributions of 1,4-dioxane concentrations in atmosphere around Plant A estimated using METI-LIS.
(4-a): meteological observatory=Kudamatsu, height of stack=10 m;
(4-b): Kudamatsu, 5 m; (4-c) Yanai, 10 m; (4-d): Yanai, 5 m.

Table 4
Results of METI-LIS estimation of concentrations in atmosphere around Plant A.

Assumption	Meteorological observation point	Kudamatsu		Yanai	
	Height of stack [m]	5	10	5	10
Estimation result	Maximum concentration [μg/m^3]	855	512	551	223
	Maximum concentration in residential zone [μg/m^3]	8.6	5.1	275	111

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residential zones was attributed to the difference in meteorological conditions, particularly wind direction, between the observatories. At the Yanai observatory, west-northwest winds accounted for more than 30% (Fig. 3), and as a result the concentrations in the east-southeast area from the emission source, which is the residential zone shown in Fig. 4, were estimated to be high. At the Kudamatsu observatory, east-northeast winds accounted for 25% (Fig. 3). In this case, 1,4-dioxane was transported mainly westward from the emission source, that is, towards the sea. Therefore, the maximum concentrations in the residential zone using the data from the Yanai observatory were estimated to be higher than those with the data at the Kudamatsu observatory.

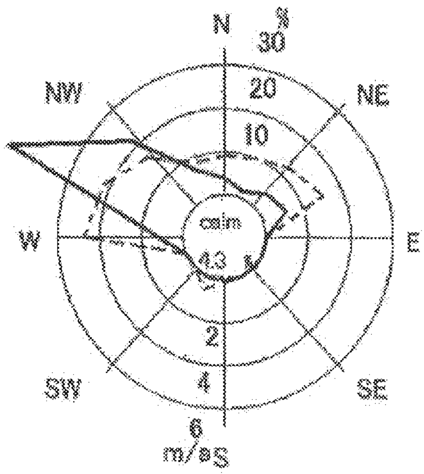
For people living near Plant A, the exposure to 1,4-dioxane was calculated to be 1.5–82.5 μg/kg/day on the basis of the estimated maximum concentration in the residential zone (Table 4), human body weight of 50 kg, and the inhalation rate of 15 m^3/day.

2.2.2 *Plant B*

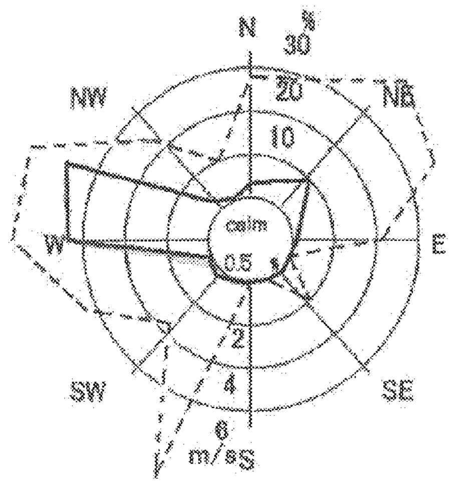
The wind roses of the Fukuda and Omaezaki observatories are shown in Fig. 5. The estimated concentration maps are shown in Fig. 6 and the estimation results are summarized in Table 5.

In the case of a 5-meter (10-meter) stack, the maximum concentration using the data from the Fukuda observatory is 26-fold (9-fold) higher than that in the residential zone using the same data. The maximum concentration according to the Omaezaki observatory data is 17-fold (5-fold) higher than that in the residential zone using the same data. Because southerly winds were rare at both observatories (Fig. 5), a small amount of 1,4-dioxane was transported north. The residential zone was assumed to be located in the northern part of this area. The maximum concentration in the residential zone, therefore, was estimated to be lower than the unconditional maximum concentration.

For people living near Plant B, the exposure to 1,4-dioxane was calculated to be 0.8–1.6



(5-a)



(5-b)

Fig. 5. Wind roses for (5-a) Fukuda and (5-b) Omaezaki in 2001. The solid line indicates the wind direction [%]. The dashed line indicates the annual average wind velocity [m/sec].

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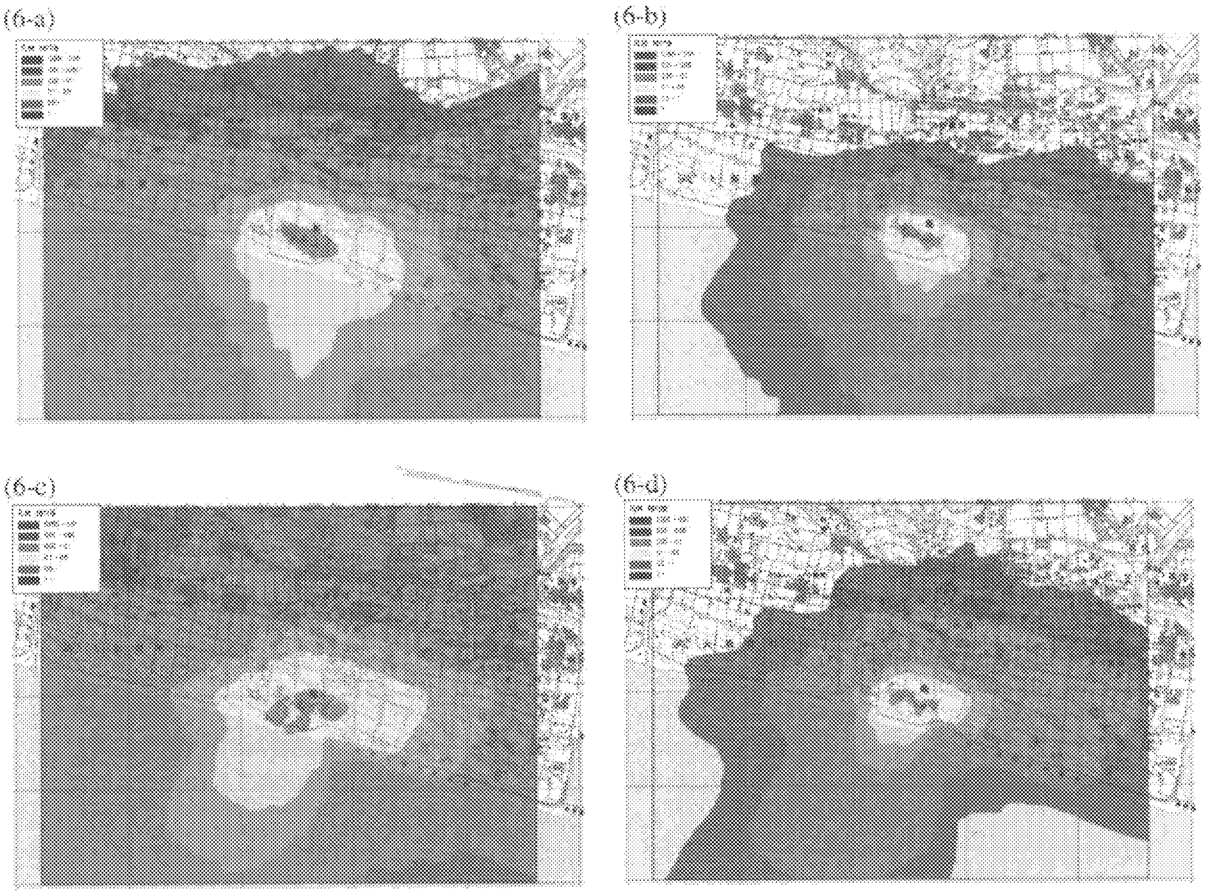

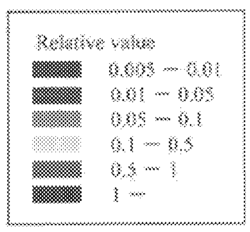

Fig. 6. Distributions of 1,4-dioxane concentrations in atmosphere around Plant B estimated using METI-LIS.
(6-a): meteorogical observatory=Fukuda, height of stack=10 m;
(6-b): Fukuda, 5 m; (6-c): Omaezaki, 10 m; (6-d): Omaezaki, 5m

Table 5
Results of METI-LIS estimation of concentrations in atmosphere around Plant B.

Assumption	Meteorological observation point	Fukuda		Omaezaki	
	Height of stack [m]	5	10	5	10
Estimation result	Maximum concentration [μg/m^3]	137	36	61	14
	Maximum concentration in residential zone [μg/m^3]	5.2	4.1	3.6	2.6

μg/kg/day on the basis of the estimated maximum concentration in the residential zone (Table 5). The same parameters were used in the calculation for the people living near Plant A. It was found that near high-volume emission sources, the extent of absorption of airborne 1,4-dioxane was overwhelmingly greater than that through consumer products (Table 3).

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3. Summary of Hazard Assessment

Although 1,4-dioxane has been reported to cause malignant tumors in more than one animal species, there is insufficient evidence for its carcinogenicity in humans according to the available human studies. Available genotoxicity studies indicate that there is no clear evidence of direct genotoxicity of 1,4-dioxane and its metabolites. There is evidence to suggest that the carcinogenicity of 1,4-dioxane may be associated with tissue damage due to cytotoxic effects followed by increased cell proliferation. The concentration of 1,4-dioxane in the blood increased in a non-linear fashion. In addition, a quantitative evaluation of 1,4-dioxane and its metabolites in the target organs of rats and humans using the Physiologically Based Pharmacokinetic Model has strongly suggested that the concentration of 1,4-dioxane in the liver increased non-linearly due to metabolic saturation.[13] Thus, the most likely carcinogenic mechanism is a non-genotoxic one through repeated cell proliferation induced by cytotoxic effects caused by the substance.[8,14,15] According to the above information, we employed the threshold approach for the quantitative assessment of 1,4-dioxane carcinogenicity in human. The oral NOAEL was determined to be 10 mg/kg/day according to two oral carcinogenicity studies in rats.[16,17] The inhalatory NOAEL reported in an animal study was 400 mg/m^3 (experimental condition: 7 h/day and 5 days/week).[18] The value was adjusted to the continuous exposure situation (24 h/day and 7 days/week) to get the inhalatory NOAEL in the general atmospheric environment; 83 mg/m^3 (= 400 mg/m^3 $\times$ 7/24 $\times$ 5/7). This corresponds to 25 mg/kg/day of exposure based on the human body weight of 50 kg and the inhalation rate of 15 m^3/day. The uncertainty factor was set at 1,000 (= 10 [interspecies variability] $\times$ 10 [interindividual variability] $\times$ 10 [tumor disease]).

4. Risk Assessment with MOE

4.1 *Use of consumer products*

In the assessment of risk from the use of consumer products, the 95th percentile of exposure was compared to the NOAEL as the worst-case scenario. The MOE calculated on the basis of the inhalation exposure and the inhalatory NOAEL was 25 [mg/kg/day]/(6.3 $\times$ 10^{-2}) [μg/kg/day] = 396,800, where the denominator was the sum of 95th percentiles for the distribution of inhalation exposure from the use of shampoos and dishwashing liquids (Table 3). The MOE far exceeded the uncertainty factor of 1,000. We therefore concluded that there is no significant health risk from inhalation exposure to 1,4-dioxane through the use of consumer products.

To assess the risk from dermal exposure, we substituted oral NOAEL, 10 mg/kg/day, for dermal NOAEL, because we could not acquire the latter in the hazard assessment. The MOE calculated on the basis of the dermal exposure and the oral NOAEL was 10 [mg/kg/day]/(3.8 $\times$ 10^{-2}) [μg/kg/day] = 263,200, where the denominator was the sum of 95th percentiles for the distribution of dermal exposure from the use of shampoos and dishwashing liquids (Table 3). The MOE far exceeded the uncertainty factor of 1,000. We therefore concluded that there is no significant health risk from dermal exposure to 1,4-dioxane through the use of consumer products.

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4.2 *Inhalation of air around high-emission plants*

Because the exposure from consumer products is negligibly small compared with that from the atmosphere around plants with high emissions, the MOEs are calculated simply by dividing the inhalatory NOAEL by the estimated maximum concentrations in the residential zone .

4.2.1 *Plant A*

MOEs were calculated by dividing the inhalatory NOAEL of 83 mg/m^3 by the estimated maximum concentration in the residential zone near Plant A. The results are shown in Table 6. The MOE calculated using the maximum concentration in the residential zone using the data from the Yanai observatory is 300 in the case of a 5-meter stack and 750 in the case of a 10-meter stack, both of which are less than the uncertainty factor of 1,000. We therefore concluded that it is possible for susceptible individuals who live near Plant A to suffer from adverse health effects, assuming that the meteorological conditions around the plant are similar to those around the Yanai observatory.

4.2.2 *Plant B*

The MOEs were calculated by dividing the inhalatory NOAEL of 83 mg/m^3 by the estimated maximum concentrations in residential zones near Plant B. The results are shown in Table 7. Because all MOEs exceed the uncertainty factor of 1,000, we conclude that there is no significant health risk from exposure to 1,4-dioxane.

5. Discussion

5.1 *Risk management*

The results of the risk assessment show that it is not necessary to take measures to reduce exposure from consumer products. As for people living near high-emission plants, the results indicate that susceptible individuals who live near Plant A may suffer from adverse health effects, assuming that the meteorological conditions around the plant are similar to those around the Yanai observatory. In this case, emission reduction measures should be taken.

Table 6
MOE calculations for residents around Plant A.

Assumption	Meteorological observation point	Kudamatsu		Yanai	
	Height of stack [m]	5	10	5	10
Estimation result	Maximum concentration in residential zone [μg/m^3]	8.6	5.1	275	111
	MOE	9,650	16,270	300	750

Table 7
MOE calculations for residents around Plant B.

Assumption	Meteorological observation point	Fukuda		Omaezaki	
	Height of stack [m]	5	10	5	10
Estimation result	Maximum concentration in residential zone [μg/m^3]	5.2	4.1	3.6	2.6
	MOE	15,960	20,240	23,060	31,920

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However, we conclude that it is not necessary for Plant A to stop the use of 1,4-dioxane immediately and that medium- to long-term emission reduction measures should be sufficient. The reasons are as follows. The MOEs are at most 3/4 or 1/3 of the uncertainty factor despite conservative assumptions about the meteorological conditions, the height of the stack, and the uncertainty factor. Moreover, the length of time during which residents near Plant A have been inhaling the air with high 1,4-dioxane concentration is only a few years, because it is only recently that the plant began to use the substance. The NOAEL, on the other hand, was obtained from the results of animal experiments to test the effect of chronic (therefore, lifetime) exposure. In addition, the latest PRTR survey results in 2003 showed that the emission of 1,4-dioxane from Plant A dramatically decreased. The present health risk of 1,4-dioxane exposure for residents near the plant, therefore, is expected to be lower.

5.2 *Estimation of concentration with METI-LIS*

In the estimation using METI-LIS of the concentrations of 1,4-dioxane in the atmosphere near high-emission plants, we used the meteorological data at observatories about 10–15 km away from each plant as a second-best approximation, because no meteorological data was available at the plants themselves. As Table 4 shows, the estimated concentrations in the residential zone were strongly influenced by the assumed meteorological conditions. If the actual meteorological conditions immediately around the plants are sufficiently different from the assumptions, the estimated concentrations cannot be used, even as a rough approximation. It is therefore important to keep in mind the dependence of the estimated exposure using concentrations projected by METI-LIS on the assumptions made about meteorological conditions, particularly if the residential zone is located in a specific direction from the source.

5.3 *1,4-Dioxane in AE-based consumer products*

In contrast to the results of this study, 1,4-dioxane was detected from AE-based consumer products in a previous study.[5] There are two explanations for this. First, ethylene oxide was polymerized under acidic conditions at the time when the previous study was published. Second, the AE-based products analyzed in the previous study also contained AES as an ingredient, without any labeling. However, we cannot verify the explanations because the previous study did not report the specific names of the products.

5.4 *Exposure from use of consumer products*

In the estimation of exposure from the use of consumer products, because the information was not available, the volume of sales of each consumer product was assumed to be the same. If we could take into account the volume of sales, the estimated interindividual variability of exposure would better reflect the actual exposure status. For instance, if a product the concentration of which is 51 mg/kg sells well and other products do not, many people will use the high-1,4-dioxane-concentration product, so the actual exposure from consumer products will be higher than the estimate in § 2.1.3. If low-1,4-dioxane-concentration products dominated the market, the actual exposure would be lower.

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5.5 *Limitation of risk assessment with MOE*

In this study, the risk assessment was conducted with MOE. The assessment with MOE is inadequate because such assessment, which we conducted in Section 4, can only estimate whether 1,4-dioxane represents a risk to human health; this means that we cannot propose a quantitative emission reduction program for 1,4-dioxane. To do this, we must express the risk in a quantitative manner, for instance, "people whose tumor incidence is 70% account for 3% of the population." The quantitative risk assessment also makes it possible to compare the risk associated with 1,4-dioxane with that associated with other substances under the concept of, for example, "Quality of Life." We would like to further assess the dose-response relationship of 1,4-dioxane using a quantitative analytical method, such as benchmark dose estimation.

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